BULLETIN OF
THE NEW YORK
ACADEMY OF MEDICINE

VOL. 11 JUNE, 1935 No. 6

THE PRINCIPLES GOVERNING THE RADIATION THERAPY OF CANCER*

(An elementary lecture)

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This treatise is not concerned with the indications and contraindications for radium and x-ray therapy nor with the relative merits of surgical and radiation treatment of cancer. It is assumed that the cancers selected for treatment by irradiation possess some degree of radiosusceptibility. Failure to consider this premise has led to the injudicious use of these physical agents with consequent loss of confidence in their effectiveness. The cancer must be more radiosensitive than the normal tissues which contain it, else radium and x-rays could offer no advantages over any destructive, non-selective cautery. The radiologist should decide if possible whether his therapeutic efforts are to be curative or palliative, insomuch as different biological and physical principles are involved. He also realizes that radiosensitivity and radiocurability are not synonymous; some highly radiosensitive tumors may become a generalized or systemic disease early in their course (lymphosarcoma) while other more radioresistant tumors metastasizing late (some neuro and liposarcomas) are radiocurable by slow progressive radiation fibrosis.

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* Read before the Stated Meeting of The New York Academy of Medicine, February 7, 1935, as a part of a symposium: The Facts About X-ray and Radium Therapy.

The selection of tumors of radiosensitive behavior for treatment by irradiation requires a knowledge of the histologic and biologic factors determining radiosensitivity, a familiarity with the natural history of malignant tumors of all regions and considerable clinical experience in observing the response of these tumors to treatment. Tumors of embryonal origin are well known to be highly sensitive to radiation due possibly to their morphologic peculiarities and high metabolic rate. There are exceptions to this rule such as the adult testicular teratoma and some tumors of mixed cell origin. The number of mitoses and the degree of anaplasia are important factors in the determination of radiosensitivity yet only in a relative sense, as some cellular, undifferentiated, rapidly growing cancers (melanoma, neurosarcoma) are notoriously resistant to irradiation. Ewing has repeatedly emphasized the importance of the influence of the intrinsic properties of the cells of origin and Stewart has succinctly stated that "in the case of many individual tumors the fundamental nature of the tissue of origin outweighs all other considerations when an attempt is made to estimate the sensitivity." Thus, the primitive blood-forming tissues predetermine the radiosensitivity of tumors developing from their lymphoid, myeloid and vascular derivatives (lymphosarcoma, myeloma, endothelioma, angioma) and the various tissues arising from the neural crest cells almost uniformly give rise to radioresistant tumors (glioma, neurosarcoma, melanoma, mixed tumor of parotid). The nature of the tissue bed supporting the cancer is of fundamental concern as every radiologist is cognizant of the difficulties and hazards encountered in irradiating cancer imbedded in cartilaginous, fat, osseous or fibrous tissue. Carcinomas are radioresistant in direct proportion to the extent of desmoplasia they excite. A soft, vascular stroma with tendency to cause a papillary structure of the tumor is more conducive to ischemic necrosis and rapid disintegration of the tumor under irradiation.

Methods of Radiation Therapy. There are two methods by which radiation may be applied to malignant tumors within the body. One uses an external source, either an x-ray tube or a radium applicator containing a large amount of radium. The rays must then traverse overlying normal tissues before reaching the tumor itself. The second method utilizes a source (radium) which is applied directly into the substance of the tumor or surrounding it. This source may be single or multiple. By this latter method the tumor receives one hundred per cent of the dose and the surrounding normal structures much less. These methods may be designated as follows:

External Radiation.

A. X-rays.
   1. Low voltage source for superficial tumors.
   2. High voltage and super-voltage sources for deep therapy.

B. Radium.
   1. Teleradium therapy. Large quantity of radium (grams) in bomb or pack applied at considerable distance (6 to 15 cm.) for deeply situated tumors.
   2. Superficial therapy. Small plaques, trays and moulages of radium for superficial cancers (lip, skin, etc.).

Intracavitary Radiation—always radium. One or more filtered containers often in tandem arrangement and placed within the body cavities for contact application of radium against cancers in these locations, such as naris, orbit, antrum, larynx, esophagus, uterus, vagina and occasionally the rectum.

Interstitial Radiation. Intratumoral or peritumoral placement of radioactive foci in form of radium needles or radon seeds. This method is useful in the treatment of accessible cancers, chiefly as an adjunct to external radiation.

Units of Dosage. It is best to administer to all the neoplastic territory the maximal quantity of radiant energy compatible with the maintenance of tissue integrity. To speak intelligently of these quantities it is best to have some common physical and biological measures of the dosage. Thus in the case of radium the quantity of gamma rays at the source is known as the "dose of emission." One knows with precision the dose of emission because this is invariable. The dose emitted is expressed by two different notations. The one has for its basis the intensity of the gamma rays and the duration of their application; the intensity is proportional to the quantity of radium present; the dose is obtained by the product of the quantity and the time, which is expressed as milligram hours of radium or as millicurie hours of radon (Gram hours or Curie hours in the case of large radium bombs or packs). The other notation, which is utilized throughout France, makes the dose proportional to the quantity of radium emanation destroyed (disintegrated) during the course of its application (Debierne and Regaud 1914). This is expressed in terms of "millicuries destroyed" or of "microcuries destroyed," the latter term connoting only one thousandth of the former. The physical efficiency of one millicurie of radon throughout its life is equivalent to 133 millicurie hours. Therefore one millicurie destroyed is equivalent to 133 millicurie hours or 133 milligram hours.

The dose of gamma or roentgen rays at the surface or the point of entrance into the body is the superficial dose while the dose to the tumor by unit volume of the tissues treated is the "tissue or tumor dose."

The unit of x-ray dosage called the "roentgen" or r unit (designated always by small r) has been standardized and internationally accepted. The roentgen has been defined as that quantity of roentgen radiation which, when the wall effect of the ionization chamber is avoided and the secondary electrons are fully utilized, produces in one cubic centimeter of atmospheric air at 0° C. and 76 cm. mercury pressure such a degree of conductivity by ionization that one electrostatic unit of charge is measured at saturation current.

In the measurement of x-rays and gamma rays by biological means the most common unit is the establishment of an erythema dose under certain conditions. Quimby of the physics department of the Memorial Hospital has defined and employed the term "threshold erythema," which is that dose of radiation that will cause a perceptible change in the skin of 80 per cent of the subjects and no discernible discoloration in 20 per cent in two to four weeks after the exposure to the rays. Quimby has found that the threshold erythema with 200 KV., 100 sq. cm. field, 50 cm. target-skin distance and filter of 0.5 mm. of copper and 2.5 mm. of aluminum is 500 to 525 roentgens. The therapeutic erythema on the other hand varies in the hands of different radiologists from 600 to 1000 roentgens.

The Tissue Dose — Cancericidal Dose. The tissue dose of a given volume of tumor is estimated according to the point within that receives the smallest quantity of energy. At the Memorial Hospital, all tissue doses are expressed in threshold erythemas. Although the quantitative basis is the best we have for tissue dosage, the response of various cancers to this same dose is qualitative and there is no absolute biologic unit to express this response. The determination of tissue doses at all depths below the skin surface and in tumors of all sizes and shapes is relatively simple with roentgen-rays and external applicators of radium. The applicator dose necessary to produce the threshold erythema can be determined in each case by direct experimentation. The percentage of the amount falling on the skin which reaches various depths can readily be determined by means of a water phantom and small ionization chamber. The tissue dose delivered in any mass by external radiation may be considered as of that point which lies deepest or at the greatest distance from the skin portal. Every radiologist has isodose curves available for each type of external radiation applicator and with this aid the determination of the depth dose for each tumor is greatly facilitated.

The problem is more complicated in interstitial irradiation. The most common interstitial sources used at the Memorial Hospital are gold seeds about 4 mm. long, 0.3 mm. in wall thickness and containing from one to three millicuries of radon. Experimental work by Quimby makes possible the determination of the percentage of a threshold erythema dose delivered at any distance from any gold radon seed imbedded in a tumor. It is necessary for every point within the region of the tumor to receive a certain minimum dose; and it is the tissue dose for the point receiving the minimum that should be calculated. It is most convenient to consider the sphere of tissue that will just contain the tumor to be irradiated. Martin and Quimby have shown that if a definite quantity of radon is to be used in any given sphere, it makes practically no difference in the dose on the periphery whether the radon be concentrated at the center or distributed uniformly within the inner half of the sphere. For purposes of approximation of dosage, they considered the radon to be concentrated at the center of the sphere that just contains the mass and calculated for the minimum the dose at a point on the periphery. Thus they were able to make a table giving the threshold erythema units for different quantities of radon in spheres of different sizes, which is of great value in the rapid calculation of dosage.

The practical value of these physical measurements is that the dosage of radiation is now on a rational rather than an empirical basis. The cancericidal doses for malignant tumors of the oral cavity, skin, breast, uterus, bladder, prostate, rectum and stomach have been determined and it is now possible to prescribe such a dose and the way it should be given, whether by external or interstitial irradiation or a combination of both methods. For example, intraoral squamous carcinomas require tissue doses of six to eight T.E.D. while transitional cell carcinomas (Ewing) and lymphoepitheliomas (Schmincke) require two to four S.E.D. for sterilization. To destroy the most radioresistant mammary cancer may require a tissue dose of ten threshold erythema units, although many radiosensitive carcinomas of the breast completely disappear after relatively small doses of external irradiation alone, when administered properly in fractionated doses.

Prescription for X-ray Therapy. A correct prescription for x-ray dosage is essential not only for purposes of record but also for the accuracy and safety of such treatments. A model prescription should mention the quantitative factor expressed in roentgens and the qualitative factor which is really the effective wave length of the beam of radiation. This may be expressed in Angstrom units or by stating the half value absorption layer of certain metallic filters. Most x-ray records are not so explicit and the effective wave length of the beam is indicated by the kilovoltage and filter employed. The target-skin distance should always be recorded and if possible the target-tumor distance or tumor depth. The size of the field, i.e., skin portal, influences greatly the proportion of scattered radiation, so the dimensions must be given for each area treated. Finally the time of application of the x-rays, whether the dose is given in a single treatment or fractionated over several days, completes the details of the prescription.

Kilovoltage (Potential). A high voltage current applied to an x-ray tube accelerates from the filament, electrons of great velocity which by their impact on the target of the tube produce the radiation known as X or roentgen rays. As the voltage is increased the average wave length of the beam of radiation becomes shorter and shorter. The shorter the wave length of the radiation the greater is the penetrating power of the beam. It is for this reason that the higher voltages (200 to 1000 KV.) are employed in deep x-ray therapy, while superficial tumors as of the skin are usually treated satisfactorily by low voltage x-rays. As the voltage is increased it has been found advisable to increase the filter accordingly in order to exclude the long, more easily absorbed and harmful rays. No x-ray beam as emitted by the target is truly homogeneous and the radiation produced in super high-voltage tubes has its quota of long, feebly penetrating rays which must be filtered out if the full effectiveness of the short-wave components of the beam is to be obtained. It has been estimated that one and a half million volts produces x-rays that approach in quality or shortness of wave length, the gamma rays of radium.

Electrostatic Production of High Voltage X-rays. The development of electric generators during the last one hundred years found its most suitable embodiment in the application of Faraday's principles of electromagnetism. Modern high voltage technic has evolved almost entirely under this influence until the present time. One of the first of the several "million volt" x-ray machines used for cancer therapy in the United States was the cascade tube designed by Coolidge, Dempster and Tanis, for operation at a maximum of 900 KV. and which was kindly loaned to the Memorial Hospital by the General Electric Company in 1931. This high voltage generator is a special induction coil to which is applied 60 cycle alternating current at a maximum of 1100 volts. Although these electromagnetic generators have been improved and the limits of their applicability in the treatment of cancer by high voltage x-rays have not been attained yet there are some valid reasons for reconsidering the possibilities of electrostatic generators. Van de Graaff was aware of the great expense, complications and inherent defects of an impulsive, alternating or rippling source of current, the necessary large size of the electromagnetic generators and the fact that the efficiency of high voltage alternating current devices decreases rapidly as higher voltages are sought. Van de Graaff therefore devised an electrostatic generator of current based on the suggestion of Kelvin that the charges could be carried to the electrode on a belt conveyor consisting of alternately insulated metal segments. His electrostatic generator required a conducting terminal, its insulating support and a means for conveying electricity to the terminal, which needs were met by a hollow metal sphere supported on an insulator and charged by a rotating belt conveying electricity from earth potential and depositing it within the interior of the sphere. He has constructed four models, three being successive developments of generators operating in air and designed respectively for 80,000,—1,500,000 and 10,000,000 volts and the fourth being an essentially similar generator operating in a highly evacuated tank. It is this last type, which when equipped with a suitable target may eventually be one of our main sources of therapeutic roentgen rays. The upper limit to the attainable voltage is said by Van de Graaff to be set by the breakdown strength of the insulating medium surrounding the sphere and its size, while the upper limit to the current is set by the rate at which the belt area enters the interior of the sphere, carrying a surface density of charge, whose upper limit is that which causes a breakdown field in the surrounding medium. Van de Graaff added a refinement to this apparatus by the addition of an induction device whereby charge of the opposite sign was carried by the belt on its return journey, thus doubling the current output. A second refinement consisted of a self-exciting charging device by means of which an external source of electricity was not needed. Although this outfit has not been used to treat cancer as yet, its perfection may well be one of the signal advances in radiation therapy.

Comparison of teleradium therapy with super-high voltage x-ray therapy. The interviews recently given to the lay press concerning the ultimate substitution of super-high voltage x-rays for radium and the consequent great economic loss to cancer institutes possessing large quantities of this valuable element are misleading and incorrect. Radium in the form of an external applicator such as a "bomb" or "pack" will probably be supplanted by roentgen therapy but the great value of radium remains as it always has been as the means of interstitial and intracavitary irradiation. External irradiation however proficient and applicable it may become will scarcely displace radium especially in its employment in emanation plants.

A comparison of teleradium therapy with an element or emanation pack and x-rays of a million volts will show little difference in biological effects with similar standards for control, if the same factors such as time of application and tissue dose delivered are considered. The million volt x-rays because of the greater intensity of radiation can treat many more patients in a given time, but this intensity may not be desirable since now we know that prolonged or continuous irradiation has many advantages. This roentgen ray outfit entails greater expense for maintenance and repairs and in some respects is less adaptable and flexible than a radium pack. The usual radium pack contains four grams of radium. If Van de Graaff's ten million volt electrostatic machine could be mounted in a vacuum and equipped with a tube, it would produce a beam of x-rays as intense as that which would emanate from an applicator containing 5,000 tons of radium. Roentgen rays produced at voltages greater than 1,500,000 are of a wave length comparable to the gamma rays of radium.

The effective wave length of radiation. The wave length of x-rays depends on two factors; the energy given to the electron and the atomic weight of the target. The greater the atomic weight of the target, the shorter will be the wave length of the characteristic radiation. The targets of most x-ray tubes used in therapy are composed of tungsten, therefore this is a fixed factor. When the x-rays enter the body the targets encountered are of low atomic weight (sodium, potassium, calcium, etc.) therefore the secondary waves or photons are of long wave length and feeble penetration. The higher the potential applied to an x-ray tube, the greater will be the energy of the impinging electron, the shorter will be the effective wave length and the greater will be the penetrating power of the beam. Therefore by increasing the potential or kilovoltage increasingly shorter wave lengths are produced, the advantage of which lies mostly in their deeper penetration and the delivery of greater depth doses to tissues. Herein is the gain achieved by the advent of super-high voltage x-rays. Failla has found that the relative depth doses at 10 cm. depth obtained under comparable conditions with 200 KV. roentgen rays, 700 KV. roentgen rays, and gamma rays, are respectively 29.0, 41.2, and 56.7 per cent. Accordingly from this point of view, 700 KV. roentgen rays are considerably better than 200 KV. roentgen rays, but not so good as gamma rays. This advantage is not realized in clinical practice because it is not practical to apply radium at the focal distances used in x-ray therapy.

Although we have said that the relative values in radiation therapy of the different wave lengths depend on their penetrating power rather than on essential differences in biological effectiveness, we do not mean that there is no differential effect on tissues. F. C. Wood states that the only difference in the electrons from very high voltage x-rays and low voltage x-rays is the difference in speed of the electron and he states that this cannot produce much difference in effect. We cannot subscribe wholly to this dogma. In the first place the number of ions produced per unit length of path of particles travelling at high speed depends on the speed of the particles. There is experimental evidence to prove the greatest concentration of ions occurs near the end of the path, when the speed of the particle is relatively low. This difference in concentration of ions depending on the speed of the electron must alter the rate of recombination of ions, which causes the chemical changes on which, presumably, radiation effects finally depend. Furthermore, we have clinical and experimental evidence to show that there is a differential action of radiation of different wave lengths in the case of normal (skin) and pathological tissues in the human body.

Ionization in Tissues. The lethal action of radiation on the cell is due to the absorbed energy, which results from the impact of the gamma or x-rays upon the atom and the release of electrons inside of the cell. The sequence of events in the cell seems to be triple; (a) ionization, (b) chemical changes and (c) biological effects. This subject having been considered in detail by Failla in his essay on "Ionization and its bearing on the biological effects of radiation," will be merely mentioned here. The initiation of the processes leading to the death of the cell is started by the transfer of energy from the beam of radiation to the matter of the cell. The phenomenon of ionization results when radiation (the particle of which is called a photon) transmits energy to an atom in its path with a resultant release of an electron traveling at high velocity and in turn expending this energy by removing still other electrons from atoms in its path. The two processes by which this transfer of energy from photons to matter takes place are (Failla[3]) : "(A) The photoelectric effect in which case all the energy of the photon is transformed at once and the secondary electron leaves the atom with a kinetic energy less than that of the photon by the amount necessary just to separate the electron from the atom, (B) the Compton effect, in which case the transfer of energy from the photon to the electron takes place according to the laws of elastic impact, and depends on the angle which the path of the emergent electron makes with the path of the impinging photon. A photon can transmit practically all of its energy to an electron in the event of a head-on collision which sends the electron hurtling through space substantially in the direction which the photon would have followed had it not been stopped. If the electron is projected in any other direction the energy imparted to it is always less than this amount; its speed is lower and the number of ions which it can produce is smaller."

No electrons can be emitted backwards towards the source of radiation and at most they can be projected only at right angles to the path of the photon. But they necessarily deviate somewhat from their initial course because of impacts with atoms in their path and so eventually after deflections and pursuance of a zig-zag trail may travel in the opposite direction. The remaining energy of the impinging photon after an electron has been set free from the atom by the Compton effect is spent as a new photon of less energy, longer wave length and less penetrating power. These photons also undergo the same transformations and on impact with atoms release their energy to electrons or beta particles which contribute to further ionization in the tissues. With an increase in the intensity of radiation, there is a corresponding augmentation in the quantitative production of ions in a given time due to the greater number of beta particle tracks, called by Failla "ionization loci." As stated previously the concentration of the ions along the tortuous path of these high speed electrons varies according to their velocity and is greatest near the end of the electron's course where the speed of the particle is relatively low.

When an atom on impact loses an electron (a negative charge), the atom then has a positive polarity and may reunite with the freed electron or any other electron in its neighborhood. The wandering electron may attach itself to an atom forming a negative ion. An interchange of electrons takes place when these ions of different polarity come together, so that neutral atoms with resultant chemical changes follow these recombinations. This process of recombination always accompanies ionization; both occur constantly in tissues which are being irradiated. Not all such effects of ionization and recombination are responsible for biological changes because the chemical transformation may be harmless to the cell. Nevertheless it seems entirely reasonable to assume that the ultimate way in which radiation affects living tissues is by these chemical changes induced by ionization and recombination.

Current (Milliamperage). The current in milliamperes and the time required to deliver a given amount of energy are inversely proportional to each other. The milliamperage is essentially a measure of the number of electrons which strike the target. The usual x-ray tubes carry from four to thirty milliamperes. Thus a tube running at four milliamperes for 25 minutes would deliver 100 milliampere minutes and a tube running at 25 milliamperes for four minutes would also deliver 100 milliampere minutes or its equivalent in roentgens, other conditions remaining the same.

Filter. The penetrating power of the radiation or the quality of the beam may be changed by the interposition of filters (usually metallic) between the tissues to be treated and the source of radiation. Soft radiation of long wave length limits the effectiveness of the beam and lessens the relative amount of the beam which reaches the deeper tissues containing the tumor. The filter will remove these soft destructive waves and permit the shorter wave lengths to pass through and enter the deeper tissues and tumor, thus affording a greater depth dosage with less skin and surface reaction. A statement of the effective wave length is one of the ways of expressing the penetrating power, or hardness or quality of the roentgen ray beam or the beam from a source of radium. The effective wave length is expressed in Angstrom units. The quality of the radiation beam may also be stated as the "half-value layer" which is the thickness in millimeters of the filter (e.g. copper) sufficient to reduce the intensity by half. Failla and Quimby have found that the effective wave length employed in the usual deep x-ray therapy at the Memorial Hospital is about 0.16 A.U. This treatment is given with 200,000 peak volts, filtered by 0.5 mm. Cu. and 1 mm. Al. With intermediate voltage of 140 KV. the filter may vary from nothing up to 6 mm. of aluminum; with a filter of 4 mm. Al. the effective wave length is about 0.25 A.U.

In the case of radium, the filters employed, usually brass, lead, silver, gold or platinum are usually expressed in the equivalents of certain thicknesses of platinum. One millimeter of platinum or its equivalent (occasionally 0. 5 mm. platinum) is the customary filter for surface applications of radium or teleradium therapy. Intracavitary radium treatments are given with filters of 0.5 to one mm. of platinum, while interstitial irradiation requires considerable less filtration. Gold radon seeds have a wall thickness of 0.3 mm. gold and most platinum needles for interstitial use are designed with a wall thickness equivalent to 0.5 mm.

Size of the field of irradiation. Failla and Quimby have derived a formula by which the amount of radiation effective at any tissue depth for all practical conditions of treatment may be obtained. This formula takes into consideration, as must all quantitative estimations of dosage, the area of irradiation or the size of the skin port. In brief we may say that the larger the field, the greater will be the secondary and scattered radiation which is produced in the body of the patient. These rays may amount to as much as 40 per cent or more of the total irradiation. At a depth of 10 cm., with a large field, probably 80 per cent of the radiation is of this type. The area treated therefore receives the sum of the primary beam plus the part of the secondary rays which traverse it. These facts are taken advantage of in therapeutics; to give as great a depth dose as possible from one or more ports (e.g. in the oral cavity) the beam is directed with great accuracy through as small a port or field as possible, since by this means the superficial dose at the port of entry may be much higher with less skin damage than when a larger port is employed.

Target-skin or radium-skin distance. The inverse square law of radiation states that the intensity of a beam of roentgen rays or gamma rays varies inversely proportional as the square of the focal-skin distance from a point source. Thus the radiation intensity from a high voltage x-ray tube at fifty centimeters distance is almost twice that delivered at seventy centimeters focal skin distance. Or a radium applicator placed at 2 cm. radium-skin distance conceivably would deliver four times the superficial dose as the same applicator applied for the same time at twice the distance or four centimeters. (This is not exactly true since the radium applicator is not a point source.) This fact may be expressed also in the following manner. Since the dose is dependent on the product of the intensity times the duration of exposure, the radium treatment at four centimeters distance would require four times as many minutes or hours as at two centimeters radium-skin distance. The question naturally arises—why not decrease the focal-skin distance as much as possible to save time and expense? In the case of very superficial non-infiltrating skin cancers this plan is feasible but for more deeply situated cancers the depth or tissue dose is increased (in comparison to the dose delivered to the superjacent skin and tissues) with the greater skin-target distance. Theoretically the distance might be increased sufficiently so that the relative dose on the skin at the port of entry of the rays would be almost the same as at the location of the tumor within the body.

Heublein method of continuous irradiation. The late Dr. Arthur C. Heublein gave the Memorial Hospital a radiation unit designed to give continuous irradiation of low intensity and short wave length to the entire body. Intermittent teleroentgen therapy had been tried previously in England and Germany with inconclusive results. This clinical experiment was carried out by Heublein and Lloyd F. Craver in 134 cases over a period of two years. Craver concluded that it was a valuable addition to the treatment of several generalized and radiosensitive tumor processes, such as the leucemias, lymphosarcoma, Hodgkin's disease and multiple myeloma, and that its results in the treatment of chronic lymphatic leucemias and pseudoleucemia seemed superior to any obtained heretofore by local irradiation. The treatment unit consists of a four bed ward with a Coolidge tube, operating at 185 KV. and 3 ma., placed near the ceiling behind the most distant wall. The patients placed at 18 feet and 24 feet from this source of radiation were continuously exposed to the beam of roentgen rays at this great distance. By an electric timing device it was determined that the patients averaged about twenty hours of exposure daily, the time out being due to nursing care and other interruptions. Considering 750 r measured in air as the clinical skin erythema dose for a single high voltage x-ray treatment, the time required to deliver a 30 per cent dose or 225 r to a patient in the bed at 24 feet target-skin distance was 250 hours, so at the rate of 20 hours of exposure daily, this dose could only be administered in 12.5 days. In the treatment of leucemia, Craver was particularly cautious but in other diseases he eventually increased the doses to 50 or 60 per cent S.E.D. (375 and 450 r) with no complications except the occasional development of leucopenia, anemia and thrombocytopenia in some cases. This work is one of the most important achievements in radiation therapy during the last decade and its principles of low intensity, great distance, continuous irradiation and long duration of treatment may soon be applicable in the local treatment of cancers that have otherwise remained refractory to present methods of applying radiation. The possible advantages, originally listed by Heublein were: "(1) the nearly uniform distribution of the rays throughout the body in treating generalized neoplasms; (2) the possibility that great protraction of treatment would make possible the irradiation of all the tumor cells during their period of mitosis when they are most sensitive and (3) the assumption that despite the protraction of treatment the intensity of radiation affecting any given cell would nevertheless remain sufficient to sterilize it."

The Time-Intensity Factor. It seems logical to assume that a cancer cell or a tissue cell would not be indifferent to variations in the intensity of radiation. Such a cell continuously engaged in self-repair, the ingestion, consumption and storage of food, the excretion of waste products, the pursuit of its specific function and possible preparation for cell division is a living unit and must be capable of making certain adjustments to the influences of noxious agents to which it is exposed, whether they be chemical or physical. All physiological processes require time for their completion. If the doses were equal, the cell—either normal tissue cell or cancer cell—should be more tolerant of prolonged irradiation of low intensity than of short irradiation of high intensity. The end result of successful external irradiation is the destruction of the cancer cell and the preservation of the normal tissue cells; there is experimental and clinical evidence to indicate that long duration and low intensity of irradiation (within limits) has greater differential effects on tumor cells than on normal tissue cells. As will be shown later, the explanation of this fact is that the normal tissues possess greater recuperative power which is taken advantage of in the increased duration of irradiation. The low intensity and longer time of irradiation permits the accumulation of a much greater total dose than could possibly be given in a single massive treatment. The tumor cannot be removed from the body for treatment by irradiation, therefore the maximum dose which can be delivered to it from external sources of radiation is limited entirely by the tolerance of the tissue which contains it.

The answer to the question whether or not the normal and cancerous tissues might vary considerably in their differential reactions to changes in the time of irradiation by roentgen rays or radium has been provided by Regaud and his collaborators—Coutard and Lacassagne. They compared the effects produced on the anorectal skin and mucosa and the testicular tissues of the rabbit and ram by selected doses of irradiation delivered in different times. The testicles of mammals were chosen for these experiments because their behavior and structure closely resemble that of malignant tissues, e.g., frequent cycles of cellular reproduction, active mitosis and radiosensitivity. This analogy between mammalian testicles (in a state of active spermatogenesis) and malignant tumors is also apparent in their response to roentgen and gamma rays. Regaud found that it was impossible to sterilize the testicles of the rabbit by the administration of a single massive dose of roentgen rays without causing serious lesions of the skin. If, without altering any of the other experimental conditions, he modified the chronological distribution of the dose, dividing it and lengthening the time of its administration, he observed a remarkable difference between the effects produced on the anorectal integuments and on those produced on the testicle. The effect on the integuments was attenuated and lessened while the effect on the testicle was increased. These studies on spermatogenesis and similar clinical experiments on the roentgen and radium treatment of epidermoid carcinomas furnished Regaud and Coutard with the data from which they formulated their theory of radiation therapy. Regaud's explanation of the superiority of continuous or fractionated irradiation over short intensive treatments is founded on the existence of alternating periods of radiosensitivity and of radioresistance in the life of the spermatogonia (in the experiments) and the cancer cell (in clinical practice). Spermatogenesis in a mammal such as the rabbit is a continuous phenomenon if the testicle is considered as a whole. But if one considers only a certain cell or line of cells on a seminiferous tubule, the function of reproduction by cell division is seen to be discontinuous and cyclic and the spermatogonia like cancer cells, pass through alternating phases of multiplication (brief phases) and of rest (long phases). In one line of cells, either spermatogonia or cancer cells, the phase of multiplication corresponds to accentuation of radiosensitivity (law of Bergonie and Tribondeau), whereas the phase of rest corresponds to a diminution in radiosensitivity. A short treatment therefore might destroy only those spermatogonia or cancer cells which are dividing at that time; it spares the others. It is only natural that prolonged and continuous irradiation (in the case of radium) or well fractionated irradiation with proper spacing of the fractions into a fairly long time (in the case of roentgen rays) is more efficient than brief intensive irradiation, because in the first case the germinal or cancer cells are killed one after the other as the cycle progresses and these cells enter for the moment the phase of maximal radiosensitivity.

These principles are now so generally recognized that the prolonged irradiation of low intensity or fractionated cumulative treatments has found almost universal favor with roentgenologists and radium therapists. These treatments depend usually on the administration of sub-erythema doses repeated every 24 to 48 hours until a total dose of six to eight threshold erythema units may be delivered to one skin portal with perfect safety. To illustrate the application of this principle, let us consider the treatment of a hypopharyngeal carcinoma by high voltage x-rays only. Two lateral ports are used to cross fire the beams of radiation. With a single massive dose, only 850 roentgens can be given to each side of the neck without seriously damaging the skin. By the fractionated method 300 roentgens may be given daily alternating on each side of the neck until a total of 3000 to 4000 roentgens are delivered through each portal. Such a course of treatment requires three weeks to consummate the dose required to sterilize the carcinoma.

Recuperation of normal and neoplastic tissues. The advantages of prolonged irradiation of low intensity or fractionated cumulative treatments are probably explained by the differential recuperation of normal and neoplastic tissues. This fact can be appreciated best by reviewing the accepted four common methods of treatment, namely (a) the massive dose technic, (b) saturation dosage, (c) fractionated dosage and (d) continuous irradiation. By the massive dose method the full tolerance of the skin and normal tissues is exhausted by a single maximal exposure to radiation, so that this dose cannot be repeated for a long time. The tumor within the tissues while profoundly affected, possibly even to a greater degree than the skin, still may survive this single dose and ultimately recover. Presumably normal tissues have much greater powers of recuperation than do neoplastic tissues, i.e., their rate of recuperation is faster. This fact can only be inferred from abundant clinical evidence at hand and from the comparative studies of Henshaw on adult and embryonal tissues. Duffy has shown that human skin can recover 69 per cent of the immediate damage in 24 hours and 76 per cent in 48 hours following the administration of a threshold erythema dose (525 r). The saturation principle was first described by Kingery who applied it in the treatment of skin diseases by unfiltered low voltage x-rays. Briefly it consists in the initial administration of an erythema dose and then maintaining the biological effect so produced by the addition of smaller doses at proper intervals. Kingery estimated that he could add 50 per cent of an erythema dose at the expiration of three and one-half days, to substitute for the 50 per cent depreciation of the original dose. Pfahler first successfully applied this principle to the treatment of cancer by properly filtered high voltage roentgen rays. In the fractionated method, previously described, a daily suberythema dose is given until a maximal effect is secured. The dose given every 24 to 48 hours is greater than the recuperation during the same period so that finally a cumulative effect is obtained. Our clinical experience leads us to believe that the results from this method are superior to the other two, possibly because the time interval and low daily dosage permits sufficient recuperation of normal tissues to maintain vitality in the irradiated part, while the more slowly recuperating cancer receives a total dose that is cancericidal. This principle has been applied by Craver still more in continuous irradiation by the Heublein teleroentgen-ray method. We may sometime find that we shall be treating cancer by the installation of numerous small x-ray units each operating at low intensity and irradiating patients through heavy filters and at relatively long distances for eight to twelve hours daily over a period of weeks. Then we should be taking full advantage of the difference in the recuperative abilities of normal and cancerous tissues.

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